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Issue: Understanding Adipogenesis and Functions of Brown Fat

Translational issues in targeting brown adipose tissue thermogenesis for human obesity management

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The recent advancements in unraveling novel mechanisms that control the induction, (trans)differentiation, proliferation, and thermogenic activity and capacity of brown adipose tissue (BAT), together with the application of imaging techniques for human BAT visualization, have generated optimism that these advances will provide novel strategies for targeting BAT thermogenesis, leading to efficacious and safe obesity therapies. This paper first provides an overview of landmark events of the past few decades that have been driving the search for pharmaceutical and nutraceutical compounds that would increase BAT thermogenesis for obesity management. It then addresses issues about what could be expected from an ideal thermogenic antiobesity approach, in particular to what extent daily energy expenditure will need to increase in order to achieve long-term weight loss currently achievable only through bariatric surgery, and whether the human body will have enough thermogenic capacity to reach this target weight loss by future therapies focused on BAT.

Keywords: obesity; diabetes; thermogenesis; energy expenditure; fat oxidation; brown fat

Introduction

With the latest projections about the global burden of obesity indicating that more than one billion people will be obese by 2030 and twice that number will be overweight,¹ the global obesity epidemic, which is the driving force behind an alarming explosion of type 2 diabetes and cardiovascular diseases, is turning into a health crisis worldwide. This grim picture is further compounded by the fact that the cornerstone method for managing obesity (i.e., dieting) has proven to be largely ineffective since few people have the willpower to adhere to the hardships of a dietary regime for a long period of time. The result is generally a transient phase of weight loss, a return on the trajectory toward obesity within a few years,² followed by repeated dieting and weight cycling, which furthers the risks for cardiometabolic diseases.^{3,4} Although in theory, an increase in physical activity could provide the solution to treat and prevent obesity, in practice, the compliance in sustaining regular exercise is also poor, and there is increased recognition of the need for alternative

or complementary strategies to enhance energy expenditure (EE). In this context, there is considerable research interest in increasing thermogenesis by targeting brown adipose tissue (BAT)—a richly vascularized tissue whose primary function, under sympathetic nervous system (SNS) activation, is to produce heat through the uncoupling of oxidative phosphorylation mediated by uncoupling protein 1 (UCP1), which is a mitochondrial protein that is unique to these cells and hence distinguishes brown adipocytes from white adipocytes and other cells.

The first era of BAT targeting

The concept of targeting BAT for obesity therapy developed in the late 1970s, following a number of classic studies in rodents suggesting that BAT is a common effector site for sympathetically mediated thermogenesis in response to both cold and diet,^{5–8} and that diminished sympathetic control of BAT contributes importantly to defective thermogenesis that underlies obesity, at least in part, in a variety of genetic, hypothalamic, and dietary animal models.⁹

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The subsequent demonstration that bilateral sympathetic denervation of interscapular BAT in lean mice (housed at 25 °C) led to greater fat deposition owing to an elevated efficiency of energy utilization (i.e., decreased thermogenesis)¹⁰ provided more direct support of a role for BAT thermogenesis pertaining to regulation of the body's fat stores.

Despite skepticism about the relevance of these findings for humans, in whom BAT was thought to be absent beyond the neonatal period, enthusiasm for targeting BAT in obesity therapy persisted throughout much of the 1980s. Indeed, anatomical and histological studies¹¹ have indicated the widespread presence of BAT in adults who died after chronic exposure to cold or from patients with pheochromocytoma (a catecholamine-releasing tumor), thereby raising the possibility that even though BAT undergoes involution after the neonatal period, it could be reactivated or induced by chronic adrenergic activation. The discovery in the 1980s of atypical (β_3) adrenoceptors¹² in BAT and white adipose tissue (WAT) of rodents and subsequently of humans, together with the findings that mice treated chronically with β_3 agonists^{13,14} showed the presence of brown adipocytes within white fat depots (now called browning of WAT) offered hope for selective targeting in the development of thermogenic drugs for the treatment of obesity.¹⁵ By the late 1990s, however, enthusiasm had waned, largely because the new drugs developed on the basis of their selectivity for the β_3 adrenoceptor in rodents and that showed marked antiobesity efficacy in rodents and dogs, had failed to fulfill the criteria of a safe and effective therapy for human obesity¹⁵—a situation that served to fuel further doubts about the recruitability and functionality of BAT in the adult human.

From pharmaceuticals to nutraceuticals

The difficulties of the pharmaceutical industry in producing drugs with good efficacy, selectivity, and pharmacokinetic properties suitable for stimulation of the small number of β_3 adrenoceptors present in humans have created and sustained a vacuum in the market for pharma-grade thermogenic products. This vacuum has long been filled by the commercialization of a plethora of herbal extracts and nutraceutical products, whose pharmacologically active ingredients—known for their actions at one or more control points along the line of SNS control

(Fig. 1)—were shown to acutely increase thermogenesis in humans and to promote fat losses associated with increased BAT thermogenic capacity when chronically administered to obese animal models. Indeed, the thermogenic effects of ephedrine, caffeine, catechin polyphenols, capsaicin-like compounds, medium-chain triglycerides (substituting long-chain triglycerides), and some specific polyunsaturated fatty acids (e.g., linoleic acid, α -linolenic acids, docosahexanoic acid, and derivatives), have been shown to be capable of stimulating UCP1 in BAT of rodents.¹⁶ The plausibility that these bioactive herbal/food ingredients, via their sympathomimetic properties, could be exerting part of their thermogenic effects through (re)activation of BAT in humans was (and still is) often underscored. Several of these compounds have been tested as pure grade compounds or as plant extracts in humans during stays in whole-body calorimeter chambers, and shown to increase 24-h EE by values ranging from 4% to 8%;^{17–23} these data are presented in Figure 2, together with those obtained for cigarette smoking²⁴ and alcohol intake.²⁵

There is currently considerable impetus for the nutraceutical and functional foods industry to capitalize on products that contain various combinations of bioactive food ingredients, particularly in light of evidence that in addition to their thermogenic properties, they may also contribute to negative fat balance through their effects in reducing fat absorption (e.g., green tea polyphenols), increasing spontaneous physical activity (e.g., caffeine), or in promoting satiety (caffeine, capsaicins, and medium-chain-triglycerides).¹⁶ Overall, however, their effects on daily EE, in amounts or at doses considered to be acceptable and safe, are very modest (50–150 kcal/day). Although they may contribute to weight control, the extra calories dissipated are clearly far from any major clinical significance in the treatment of obesity.

The second era of BAT targeting

During the past few years, the notion of targeting BAT for enhancing thermogenesis in human obesity therapy has been revitalized by a spate of landmark discoveries. First, the application of radiodiagnostic techniques (positron emission tomography (PET)/computed tomography (CT)), coupled with histology studies, to healthy humans have identified the presence of metabolically active BAT that

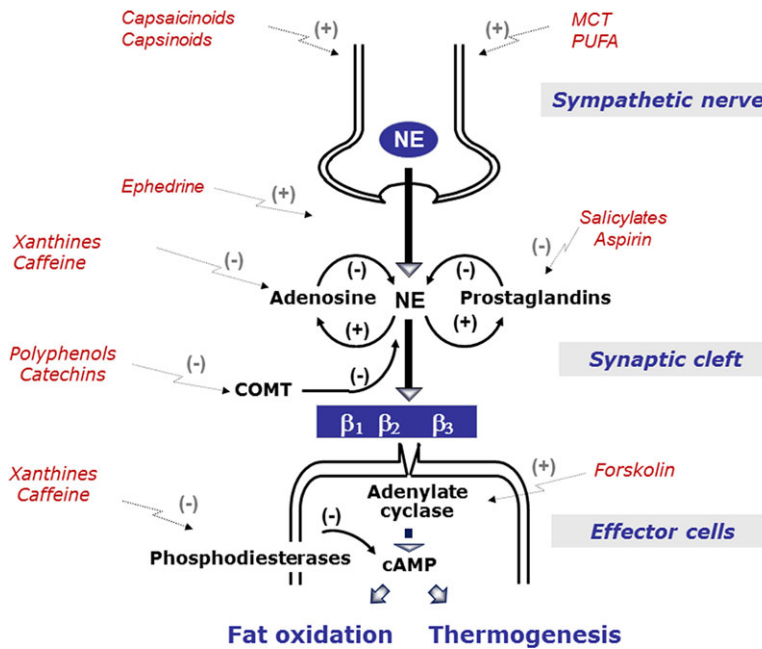


Figure 1. Mechanisms by which bioactive food/herbal ingredients may modulate sympathetic control of thermogenesis. Sympathetically mediated norepinephrine (NE) release and actions (via β adrenoreceptors) are under negative-feedback modulation by (1) adenosine, certain prostaglandins, and catechol-*O*-methyl transferase (COMT) in synaptic neuroeffector junction; and (2) at the cellular level by phosphodiesterases, which break down NE-induced cyclic adenosine monophosphate (AMP). Thus, when NE release is enhanced pharmacologically (e.g., by ephedrine) or by food ingestion, the inhibitory effects of adenosine, COMT, and phosphodiesterases on further NE release and actions could be opposed by xanthines (e.g., caffeine), salicylates (e.g., aspirin), or flavonoid polyphenols (e.g., green tea catechins). Thus, the stimulatory effect of NE on thermogenesis and fat oxidation could be increased and/or prolonged. Adapted, with permission, from Dulloo.¹⁶

becomes apparent (mostly in the supraclavicular and paravertebral regions) by relatively short exposure to mild cold.^{26–30} Second, studies in genetically engineered murine models have established that the development of BAT thermogenic capacity for adaptive thermogenesis involves not only processes of recruitment through hypertrophy and hyperplasia of classic brown adipocytes in defined anatomical BAT depots, but also by processes that induce the browning of WAT.³¹ The latter is defined as the appearance of functional brown adipocytes in WAT after chronic thermogenic stimulation and referred to as brite (brown-in-white) or beige adipocytes. Third, and what seems pivotal in the search for molecular targets in activating BAT thermogenesis, are the demonstrations that these two types of brown adipocytes (classic vs. brite) may derive from distinct precursors and possess distinct molecular signatures. Whereas the classic developmentally programmed brown adipocyte arises from mesenchymal precursor cells common to the myogenic cell

lineage, the brite/beige adipocyte derives from precursor cells that are closer to the white adipocyte cell lineage.³² Some have argued, however, that this process of browning of WAT may also involve trans-differentiation processes of white-to-brown adipose cells.^{33,34} Whatever their developmental origins, the observations that human BAT may derive predominantly from the browning process and that the formation of brite/beige adipocytes is induced not only in response to SNS activation, but also to a variety of endocrine factors secreted by the liver (e.g., fibroblast growth factor 21), skeletal muscle (e.g., irisin) and heart (e.g., natriuretic peptides), have highlighted the potential relevance of brite/beige adipocytes in determining the total BAT thermogenic capacity in humans.³⁵

There is considerable optimism that a better understanding of how these newly identified endocrine factors, which control the signaling pathways that activate classic BAT or induce browning of WAT (or both), will pave the way for novel therapeutic

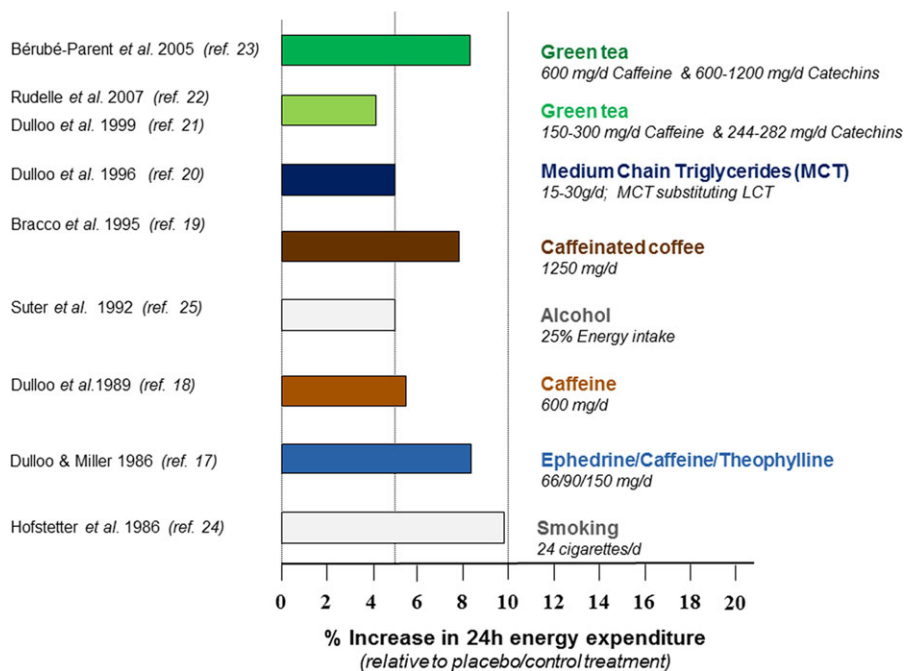


Figure 2. Percent increase in 24-h energy expenditure, assessed in indirect calorimetry (respiration) chambers, in response to drugs and other compounds and extracts screened for thermogenic properties (reviewed in detail in Ref. 16).

opportunities to stimulate BAT thermogenesis. There are, however, a number of issues of central importance that need to be considered when developing an ideal thermogenic antiobesity approach. Several of these issues emerged during the first era of BAT targeting and are now examined in light of the current state of knowledge about the relative efficacy of various forms of obesity therapy, human energy metabolism, and the biology of BAT.

How much of an increase in daily EE should we aim for?

Independently of future approaches to recruit or induce BAT thermogenesis, whether by pharmacological,¹⁵ nutraceutical,^{16,36} or transplantation therapy,³⁷ an issue of cardinal importance concerns the extent to which whole-body thermogenesis should be stimulated in order to achieve clinically significant weight loss. It is clear that the attribution of efficacy to any thermogenic approach for weight loss therapy would require that this approach is successful in achieving long-term weight loss. In this context, weight loss efficacy will certainly be measured against that of bariatric surgery, which is the only treatment for obesity resulting

in an average of more than 15% long-term weight loss documented over 10–15 years, namely in the Swedish Obesity Subjects (SOS) trial.³⁸ In absolute terms, this efficacy of bariatric surgery amounts to long-term weight loss of 20 kg on average. The question arises as to how much daily EE would have to be increased by an ideal thermogenic approach in order to reach similar long-term weight loss? The answer to this question is discussed below from an analysis of the fall in EE (energy gap) that would arise following a 20-kg weight loss achieved by dieting in an average obese individual.³⁹

Energy gap for weight maintenance after 20-kg weight loss

From a purely thermodynamic standpoint, a loss in body weight will entail obligatory reductions in several compartments of daily EE, in particular (1) less energy would be required to sustain basal metabolism, since resting metabolic rate (RMR)—the major component of daily EE—is a function of body mass and in particular lean body mass, and the weight lost includes not only fat but also lean body mass; (2) less energy would also be required for the amount of energy spent in performing

physical activity since from a consideration of simple mechanics, it costs less energy to move a lower body mass; and (3) less energy would be dissipated as the thermic effect of food since less food is consumed during dieting.

Furthermore, it has been shown that body weight is a good predictor of total 24-h EE in sedentary subjects:⁴⁰ the more severe the obesity, the greater the daily EE, not only because of the higher lean body mass and basal metabolic rate, but also because of an increase in the energy cost of weight-bearing activities (e.g., standing, walking, and spontaneous movement) as this cost is related to body weight. Limitations in the accurate measurements of body composition during weight changes notwithstanding,⁴¹ the available evidence also suggests that the composition of excess weight gain in the obese seems to be within the same range as the composition of weight loss induced by dieting, namely 70–80% fat and 20–30% fat-free mass.^{42,43} It therefore follows that the slope of the linear regression observed between body weight and 24-h EE (assessed cross-sectionally in sedentary individuals using respiration chambers) provides a crude estimate of the change in daily EE associated with each kg change in body weight, namely 20 kcal/kg/day on average.^{40,44,45} On the basis of these estimates, it can be calculated that a weight loss of 20-kg body weight in an obese patient will result in an obligatory average reduction of 400 kcal in daily EE. Besides this obligatory or passive energy economy, further reductions in daily EE can also be expected as it has repeatedly been demonstrated that the fall in EE is greater than predicted by the loss of body mass, thereby underscoring the operation of mechanisms that actively promote energy conservation through adaptive suppression of thermogenesis.

In a review about the clinical significance of adaptive thermogenesis during weight loss, Major *et al.*⁴⁶ point to several weight reduction programs, including those that incorporate both diet and exercise, where values of 100–220 kcal/day on average could be ascribed to adaptive thermogenesis in the fall of sedentary EE assessed as postabsorptive RMR and/or sleeping EE. Furthermore, such adaptive suppression of thermogenesis could also operate to spare energy in the nonresting compartment of daily EE, as judged by 10–27% increases in the mechanical efficiency of walking or cycling following weight

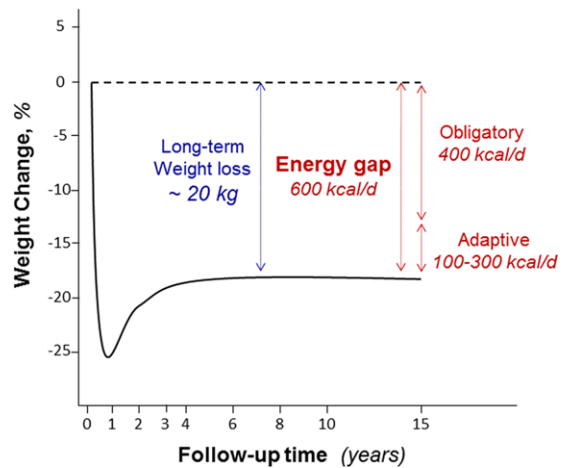


Figure 3. Schematic diagram illustrating long-term weight losses, based on the results of the Swedish Obesity Subjects (SOS) bariatric surgery study.³⁸ The broken line represents the control patients. Shown is the energy gap for long-term maintenance, subdivided into components that represent passive (obligatory) and active (adaptive thermogenesis) components.

loss, all of which would contribute to a further reduction in energy needs. Our more recent analysis of the literature indicates that the energy economy due to adaptive thermogenesis in the fall in total EE (resting + nonresting) would be in the range of 100–300 kcal/day.⁴⁷ Overall, therefore, the addition of the latter values for the adaptive fall in daily EE to the obligatory reduction of 400 kcal/day following a 20-kg weight loss in obesity therapy will entail an energy gap amounting to 500–700 kcal/day (Fig. 3). Consequently, any approach that relies primarily on increasing thermogenesis for achieving similar levels of long-term weight loss achieved by bariatric surgery will have to be effective in stimulating daily EE by approximately 600 kcal daily, assuming no change in energy intake. This is far above any increase in 24-h EE documented so far in the search for thermogenic compounds, which at safe doses were found to be less than 150 kcal/day. The critical question at this point is whether the adult human body possesses such a capacity for thermogenesis that could be exploited by future therapy.

Human capacity for nonshivering thermogenesis

Adult humans clearly have the capacity to mount substantial increases in nonshivering thermogenesis (NST) when acclimatized to cold. In the most

recent cold-acclimation study,⁴⁸ young adults were wrapped in a water-perfused suit and exposed to temperatures of 15–16 °C for 6 h daily for 10 consecutive days. The acute cold-induced NST expressed as a percent of resting EE was shown to increase from 11% before cold acclimation to 18% at the end of the 10 days of cold exposure (i.e., NST amounted to 175 kcal/day before and 290 kcal/day after 10 days of cold acclimation). A much greater capacity for NST was observed in the classic cold chamber experiment of Davis,⁴⁹ conducted in young subjects wearing only shorts when acclimatized to a colder environment (12 °C) and for longer duration (8 h/day for 31 days). Indeed, after the first week of cold acclimation, during which shivering activity was found to decline rapidly, the cold-induced elevation in metabolic rate was sustained throughout the one-month study, thereby implicating the recruitment of large increases in NST for thermal regulation to explain the 34% increase in metabolic rate. Translated to daily EE, such an increase in metabolic rate would amount to a capacity for NST that exceeds 600 kcal/day. On the basis of this analysis, the case can be put forward that adult humans have the capacity to increase thermogenesis to meet the goal of the ideal thermogenic strategy for achieving long-term weight loss of some 20 kilograms. How much of this thermogenic capacity can be achieved through BAT heat production per se and how much BAT mass would be required to reach this level of thermogenic capacity are issues that are addressed below.

Quantitative contribution of BAT to whole-body thermogenesis

From the recent study of cold acclimation mentioned above,⁴⁸ the findings from PET/CT scanning that BAT activity (assessed by fluorodeoxyglucose (FDG) radiotracer uptake) increased in parallel with the increase in NST following cold acclimation is certainly consistent with an important role for BAT recruitment in NST in adult humans after repeated intermittent cold exposures. Evidence for consistency through associations, however, is not evidence for causality. Nonetheless, those who advocate a quantitatively important contribution of BAT thermogenesis to cold-induced NST point to the calculations of Rothwell and Stock,⁵⁰ which are based on data about the high metabolic rate of this tissue in response to norepinephrine in hyperphagic rats exhibiting diet-induced thermogenesis (1.7 mL

O₂/g/min). On the basis of these calculations, they have proposed that the activation of 40–50 g of active BAT by norepinephrine in an average sedentary man spending 2500 kcal/day would indeed correspond to an increase of about 20% in daily EE. Thus, an apparently trivial amount of BAT, if activated, could have a profound influence on energy balance, since 10–20% of daily EE (i.e., 250–500 kcal/day) can make the difference between maintaining body weight or gaining 10–20 kg within a few years.

There are, however, several counterarguments to these calculations. In a revisit of these rat-to-human data extrapolations, van Marken Lichtenbelt and Schrauwen⁵¹ have questioned these estimates on the basis of the allometric differences between small rodents and humans, while also underscoring that maximal BAT stimulation is unlikely to be reached under physiological conditions. They argue that 50 g of active BAT in humans could contribute to only 3–5% of basal metabolic rate. These values are in accord with the conclusions reached by Virtanen *et al.*²⁸ using glucose-uptake estimates made during PET/CT scanning in a study where BAT activity was found to contribute to 4.5% of BMR in subjects acutely exposed to cold. An even lower contribution of BAT thermogenesis to the whole-body EE in response to acute cold exposure (16 °C) in humans has been reported by Muzik *et al.*⁵² who used dynamic oxygen-15 PET imaging to study oxidative metabolism in BAT depots based on independent measurements of both blood flow and oxygen extraction. BAT thermogenesis was found to account for less than 2% of the increase in whole-body EE (i.e., less than 20 kcal/day) even in subjects showing relatively large BAT activity (assessed by FDG tracer uptake) and large increases in whole-body EE of approximately 300 kcal/day on average. According to these authors,⁵² these results beg the questions of whether the glucose that is transported in human BAT during cold exposure is stored, oxidized, or released as lactate, and whether the elevated FDG uptake in BAT is an epiphenomenon. Furthermore, because of large differences in blood flow and glucose oxidation in BAT between humans and rodents, the extrapolation of rodent data to humans may lead to erroneous conclusions.

How much BAT do humans possess?

Estimates of the mass of BAT vary considerably across studies, with some reports showing that

values for the total volume of BAT amount to less than 50 g in most individuals, while others reporting values in the range of up to 100–200 grams.²⁸ The figure depends critically on the type and intensity of prior cold exposure and on the definition criteria for the positive BAT FDG uptake. Furthermore, it should be emphasized that human BAT depots contain a mixture of brown adipocytes interspersed within a greater volume of white adipocytes that have much lower metabolic activity. Although measures of BAT by FDG uptake and PET/CT have so far been considered the gold standard, this technique is limited by poor reproducibility and insufficient resolution to localize microscopic patches of brown adipocytes. As emphasized by Muzik *et al.*,⁵² PET imaging provides an average metabolic activity of a mixed cell population within the anatomically defined depot, such that the low average activity of human BAT depots may reflect the relatively low density of brown adipocytes. Indeed, the presence of UCP1 in supraclavicular adipose tissue has been revealed even when the results of PET/CT scans are negative⁵³ (most likely due to suboptimal sensitivity of standard PET/CT), thereby reinforcing the contention that the prevalence of BAT is higher than so far recognized in adult humans, and the potential for its recruitment and induction by future thermogenic therapies remains plausible. But whether such recruitment/induction will translate into a major contribution to the level of whole-body thermogenesis required for clinically significant therapeutic weight loss will have to await further development of more refined tools for human BAT detection and functional state assessment.

UCP1-independent nonshivering thermogenesis

It should be emphasized that UCP1-independent thermogenic mechanisms and other organs and tissues can also be recruited for NST. When housed at low temperatures (20 °C) and fed a high-fat diet, mice deficient in UCP1 are more resistant to obesity than wild-type controls without consuming less food,⁵⁴ thereby underscoring the recruitment of alternative thermogenic mechanisms, which could be associated with increased oxidative capacity in WAT.⁵⁵ One should also recall the studies of blood flow coupled with regional arteriovenous oxygen differences conducted by Foster and colleagues in the 1980s,^{56,57} which indicated that

interscapular BAT oxygen consumption, although increased markedly by cold exposure, was not induced in rats exhibiting diet-induced thermogenesis in response to cafeteria overfeeding.⁵⁶ Subsequent studies underscored a quantitatively important role for the liver in the mediation of the adaptive increase in thermogenesis in response to caloric excess.⁵⁷

Cardiac responses to stimulation of thermogenesis

A concern that is often raised about strategies to manage obesity by targeting thermogenesis is that it will result in an increased heart rate. Indeed, as EE increases, the work done by the heart must also increase to meet the body's greater demand for oxygen. During exercise, there is a fairly close relationship between heart rate and EE, to the extent that the field technique for continuously measuring heart rate has been used to estimate EE in humans. However, the relationship between EE and heart rate is curvilinear, and at low levels of increased EE (less than twofold), heart rate does not increase as steeply for a given change in EE, probably due to changes in stroke volume. Consequently, an increase in heart rate in response to an extra demand in oxygen resulting from a 25% increase in daily EE is likely to be marginal. To put this into context, simply chewing gum (8.4 g, energy-free) increases EE by approximately 20%,⁵⁸ and in our laboratory, intermittent leg-press exercise of low intensity (while comfortably seated) increased EE by 65%, with heart rate increasing by only 5–7 beats/min.⁵⁹

Impact of increased thermogenesis on appetite

It has long been known, from studies conducted both in humans and in animal models, that two of the most potent stimuli of heat production—the thyroid hormones and exercise—increase food intake, and the case is often put forward that future thermogenic strategies could also be limited by compensatory increases in food intake. However, the view that targeting thermogenesis will almost inevitably lead to a compensatory increase in food intake is not supported by the data gathered over the past decades in the search for thermogenic stimulants. Neither the numerous β_3 adrenoceptor agonists that have been screened,¹⁵ nor the

administration of the bioactive food ingredients with thermogenic properties,¹⁶ led to increased food intake in obese animals; if anything, energy intake tended to be lower in some cases.

Conclusions

On the basis of the analysis of human data on the activation of NST during cold acclimation, humans have the potential to increase their whole-body thermogenic capacity to achieve long-term weight loss currently achievable only through bariatric surgery. The quantitative contribution of BAT to this thermogenic capacity is at present uncertain, but judging from the anatomic and histological data of adult humans who died from chronic cold exposure or from some patients with pheochromocytoma, the recruitability/induction of BAT can be impressive under chronic stimulation. With the current surge in research focused on unraveling the biology of BAT, and with likely advances in human BAT detection and activity assessment by PET/CT technology coupled to magnetic resonance imaging (MRI) techniques, there is no doubt that new therapeutic avenues for research will continue to develop toward enhancing thermogenesis by BAT targeting. The enthusiasm to move along these research avenues is further driven by the notion that even if the weight loss efficacy of these future therapeutic approaches prove to be modest, the role of BAT as a sink for glucose and lipid utilization may prove to be efficacious for the long-term management of type 2 diabetes and other obesity-associated comorbidities. Amidst such excitement and optimism that this second era of BAT targeting would materialize into the development of effective and safe thermogenic antiobesity and/or antidiabetic therapies, a few words of caution might seem somewhat misplaced. But as recent history in the field of obesity has taught us, whether when dealing with transgenic mice in assessing the role of UCP1, UCP2, or UCP3 in weight homeostasis; when translating promising research findings from rodents and dogs to humans (the β_3 agonist failures); or when “successful” clinical trials translate into therapeutic fiascos (such as that associated with rimonabant); we need to be prepared to expect the unexpected and hope that our motivation to put “fat in the fire” does not backfire on the century-old concept of treating obesity by stimulating thermogenesis.

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Conflicts of interest

The author declares no conflicts of interest.

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